

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
 )  
Luc CHANTELOUP et al. )  
 )  
Serial No.: To Be Assigned ) Group Art Unit: To Be Assigned  
 )  
Filed: Herewith ) Examiner: To Be Assigned  
 )  
For: INTERMEDIARY COMPOUNDS )  
FOR THE HEMISYNTHESIS OF )  
TAXANES AND PREPARATION )  
PROCESSES THEREFOR )

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

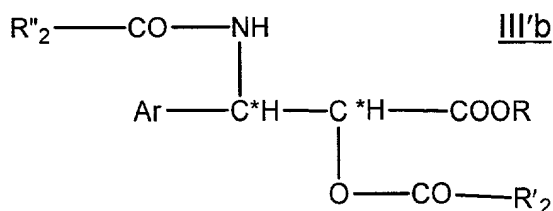
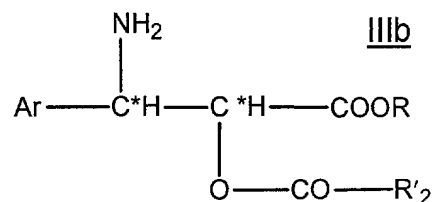
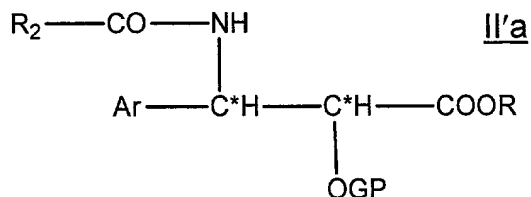
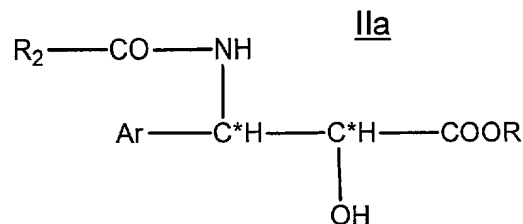
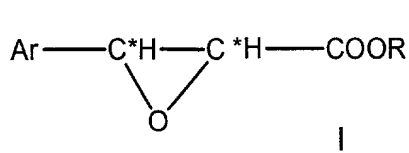
PRELIMINARY AMENDMENT

Prior to examination on the merits, Applicants hereby request that Examiner enter the following amendments.

IN THE CLAIMS:

Please cancel claims 1-11, 15, 16, and 25 without prejudice or disclaimer thereof, and please amend claims 12-14, 17-24, and 26 as follows:

12. (Once Amended) A precursor compound of at least one taxane side chain, wherein said precursor compound comprises at least one compound of formulae I, IIa, II'a, IIIb and III'b, or derivatives thereof:



wherein

Ar is an aryl radical, R<sub>2</sub> is an aryl radical, R'<sub>2</sub> is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical, R''<sub>2</sub> is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical, and GP is a protective group, and

R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical.

13. (Once Amended) A compound according to one of claims 12 or 14, wherein R is a menthyl radical enantiomer, optionally (+)-menthyl.

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FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
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202-408-4000

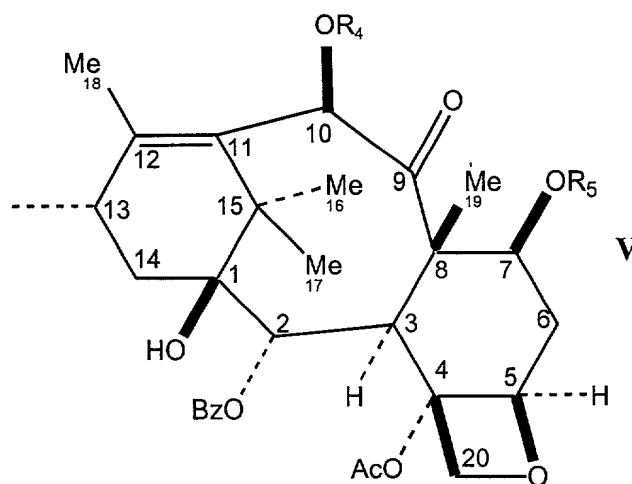
14. (Once Amended) A compound according to claim 12, wherein the cis- $\beta$ -phenylglycidate derivative of general formula I is of (2R,3R) configuration, and the derivatives of general formulae IIa, IIIb and III'b are of (2R, 3S) configuration.

17. A process for preparing a taxane of general formula IV,

C-B IV

wherein

B represents a radical of general formula V



wherein

Ac is an acetyl radical,

Bz is a benzyl radical,

Me is a methyl radical,

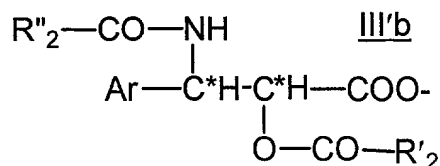
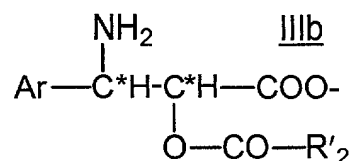
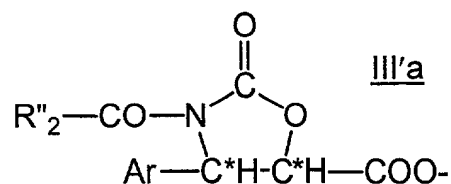
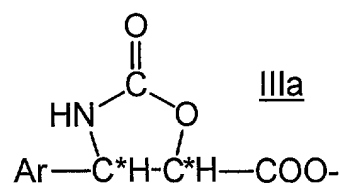
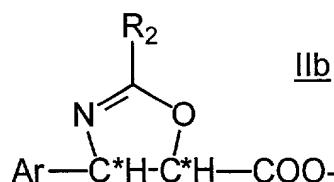
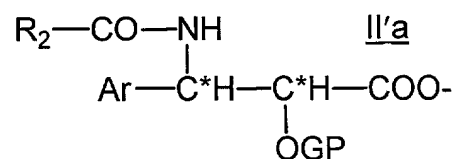
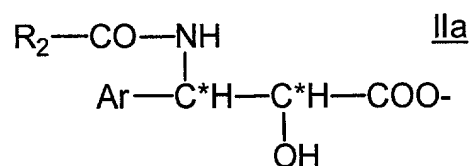
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$R_4$  is an acetyl radical, or a protective group for the hydroxyl functional group, represented by GP1,

$R_5$  is a protective group for the hydroxyl functional group represented by GP2, wherein GP1 and GP2 are chosen independently of one another from conventional protective groups employed in a hemisynthesis of taxanes, and

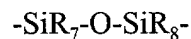
C is a side chain chosen from formulae IIa, II'a, IIb, IIIa, III'a, IIIb, and III'b:



wherein Ar is an aryl radical,  $R_2$  is an aryl radical,  $R'_2$  is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical,  $R''_2$  is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical, and GP is a protective group, comprising esterifying an appropriate baccatin III derivative of general formula V, carrying a C-13 hydroxyl functional group, with a derivative of

formulae IIa, II'a, IIb, IIIa, III'a, IIIb, or III'b, wherein R represents a hydrogen atom, and is obtained by controlled saponification.

18. (Once Amended) A process according to claim 17, wherein the GP1 and GP2 protective groups are independently chosen from trialkylsilyls, TROC, linear or branched bulky haloalkoxycarbonyl radicals comprising at least one halogen atom, acyl radicals in which the carbon  $\alpha$  to the carbonyl functional group carries at least one oxygen atom, or a trialkylgermanyl radical, or GP1 and GP2 together form a divalent radical of formula

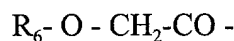


wherein

$\text{R}_7$  and  $\text{R}_8$ , independently of one another, each represent a sterically hindered alkyl radical.

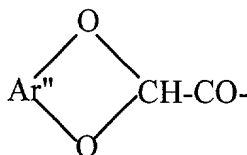
19. (Once Amended) A process according to either one of claims 17 or 18, wherein the acyl radicals in which the carbon  $\alpha$  to the carbonyl functional group carries at least one oxygen atom are chosen from

- alkoxy- or aryloxyacetyl radicals of formula



wherein  $\text{R}_6$  is a sterically hindered alkyl radical, a cycloalkyl radical, or an aryl radical,

- or arylidenedioxyacetyl radicals of formula



wherein Ar" represents an arylidene radical.

20. (Once Amended) A process according to claim 19, wherein:

the sterically hindered alkyl radical is a linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl radical, substituted by at least one bulky substituent chosen from halogens, linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and aryl radicals,

the cycloalkyl radical is a C<sub>3</sub>-C<sub>6</sub> cycloalkyl radical, optionally substituted by at least one bulky substituent independently chosen from halogens, linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy, and aryl radicals,

the aryl radical is a phenyl, naphthyl, anthryl or phenanthryl radical, optionally substituted by at least one bulky substituent chosen from halogens, linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy, or aryl radicals, and

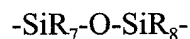
the arylidene radical is a phenylene, naphthylene, anthrylene or phenanthrylene radical, optionally substituted by at least one bulky substituent chosen from halogens, linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy, and aryl radicals.

21. (Once Amended) A process according to either one of claims 17 or 18, wherein R<sub>4</sub> represents an acetyl radical, and GP2 is chosen from a trialkylsilyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2,2,2,1-tetrachloroethoxycarbonyl, 2,2,2-trichloro-*t*-butoxycarbonyl, trichloromethoxycarbonyl, phenoxyacetyl, and trialkylgermanyl radicals.

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FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

22. (Once Amended) A process according to either one of claims 17 or 18, wherein  $R_4$  represents a GP1 group, and GP1 and GP2 are independently chosen from a 2,2,2-trichloroethoxy-carbonyl and a phenoxyacetyl radical, or together form a divalent radical of formula



in which  $R_7$  and  $R_8$  each represent an isopropyl radical.

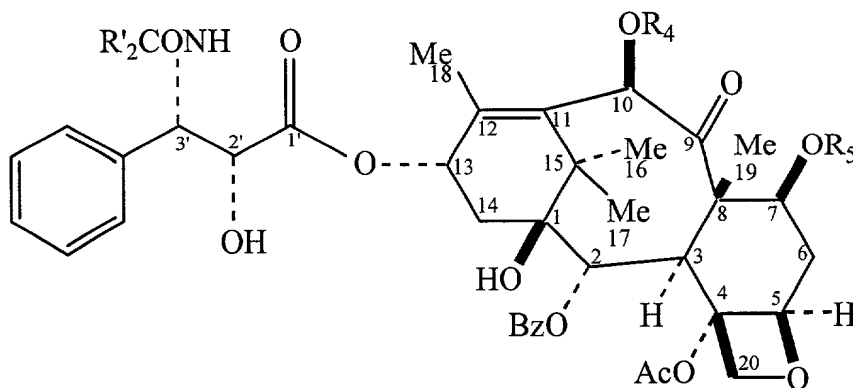
23. (Once Amended) A process according to claim 17 or 18, wherein

C is a radical of formula IIa with Ar; and

$R_2$  is a phenyl radical; and

$R_4$  is an acetyl radical.

24. (Once Amended) A process according to claim 17 or 18, further comprising deprotecting the hydroxyls of the derivatives of general formula IV and optionally, simultaneously or separately, opening the oxazoline ring of the radicals of formula IIb or IIIa wherein a taxane derivative of general formula VI is produced



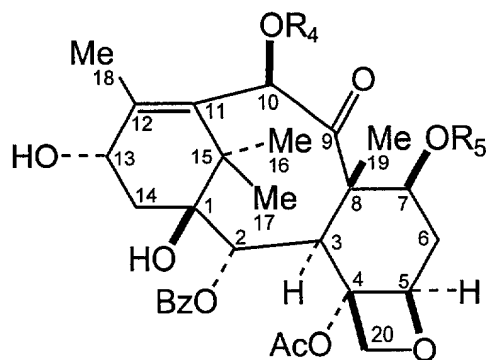
wherein

Ac is an acetyl radical, Bz is a benzyl radical, Me is a methyl radical, and R'<sub>2</sub> is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical,

R<sub>4</sub> represents a hydrogen atom or an acetyl radical, and

R<sub>5</sub> represents a hydrogen atom.

26. (Once Amended) A baccatin III derivative which is of use in the hemisynthesis of taxanes, chosen from derivatives of general formula V



wherein

Ac is an acetyl radical,

Bz is an benzyl radical,

Me is a methyl radical,

R<sub>4</sub> is an acetyl radical or a protective group for the hydroxyl functional group represented by GP1,

R<sub>5</sub> is a protective group for the hydroxyl functional group represented by GP2, wherein

GP1 and GP2 are selected independently of one another from

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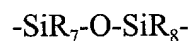
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& DUNNER, L.L.P.  
1300 I STREET, N. W.  
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bulky haloalkoxycarbonyl radicals, with the exception of TROC, acyl radicals in which a carbon  $\alpha$  to the carbonyl functional group carries at least one oxygen atom, and trialkylgermanyl radicals, or

GP1 and GP2 together form a divalent radical of formula



wherein

$\text{R}_7$  and  $\text{R}_8$ , selected independently of one another, represent a sterically hindered alkyl radical.

Please add the following new claims:

- 27. The method of claim 20, wherein the cycloalkyl radical is cyclohexyl, optionally substituted by at least one linear or branched  $\text{C}_1\text{-C}_6$  alkyl radical.
28. The method of claim 27, wherein the cyclohexyl radical is selected from menthyl, its enantiomers, and mixtures of its enantiomers in any proportion.
29. The method of claim 20, wherein the aryl radical is substituted by at least one phenyl radical.
30. The method of claim 29, wherein said at least one phenyl radical is substituted by one or two bulky substituents ortho- and ortho'- to the ether bond.

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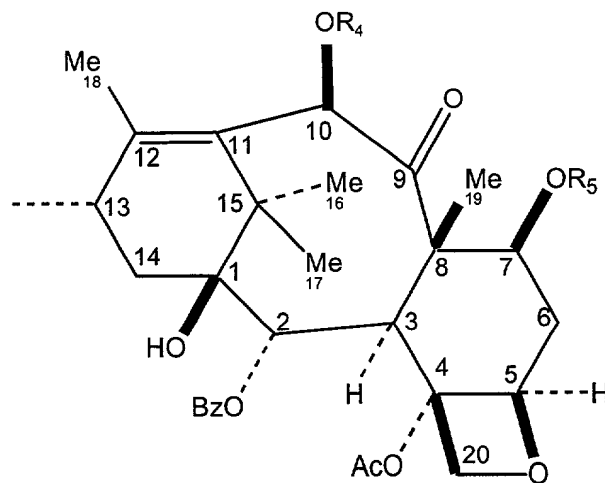
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1300 I STREET, N. W.  
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31. The method of claim 20, wherein the arylidene radical is substituted by at least one phenyl radical.

32. A taxane derivative of general formula IV

C-B IV

wherein B is a radical of general formula V:



wherein

Ac is an acetyl radical,

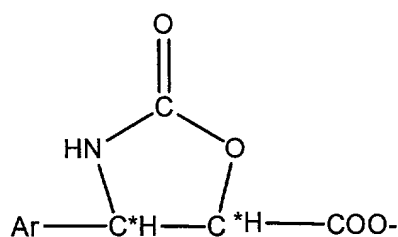
Bz is an benzyl radical,

Me is a methyl radical,

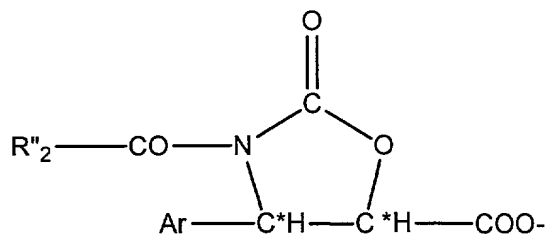
R<sub>4</sub> is an acetyl radical, or a protective group for the hydroxyl functional group,

represented by GP1, and

$R_5$  is a protective group for the hydroxyl functional group represented by GP2, wherein GP1 and GP2 are selected independently of one another from conventional protective groups employed in the hemisynthesis of taxanes; and wherein C is a side chain selected from formulae IIIa and III'a:



IIIa



III'a

wherein Ar is an aryl radical, and  $R''_2$  is chosen from an aryl radical, a lower alkyl radical, and a lower perhaloalkyl radical.

33. The taxane derivative of claim 32, wherein said conventional protective groups employed in the hemisynthesis of taxanes are chosen from trialkylsilyls and TROC.--

### REMARKS

Claims 1-11, 15, 16, and 25 have been cancelled, claims 12-14, 17-24 and 26 have been amended, and new claims 27-33 have been added; therefore claims 12-14, 17-24, and 26-33 are pending. Support for these claims occur in the specification and claims as filed. The

amendments correct matters of language and form, or correct improper dependency, and as such introduce no new matter, and do not narrow the scope of the claims in any way.

Specifically, new claims 27-31 represent matter deleted from claim 20 as filed. New claims 32 and 33 correspond to the subject matter of originally filed claim 25, rewritten in independent form with a proper dependent claim. The amendments therefore introduce no issue of new matter and Applicants respectfully request their entry.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

Dated: April 18, 2001

By: Carol P. Einaudi  
Carol P. Einaudi  
Reg. No. 32,220

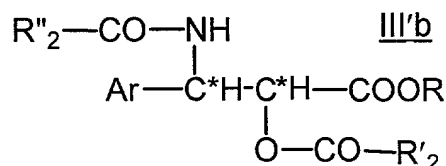
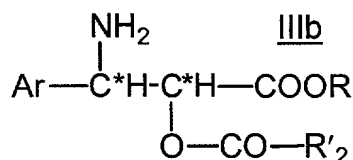
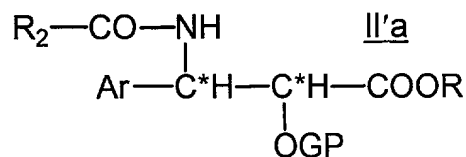
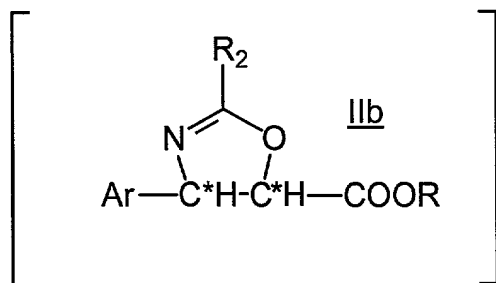
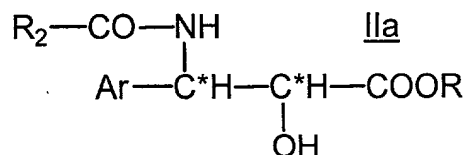
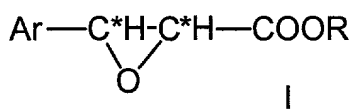
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& DUNNER, L.L.P.  
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## APPENDIX OF AMENDMENTS TO CLAIMS 12-14, 17-24, AND 26

12. (Once Amended) [Precursor compounds of taxane side chains, characterized in that they]

A precursor compound of at least one taxane side chain, wherein said precursor compound comprises at least one compound of [are selected from the derivatives of following general formulae I, IIa, [IIb,] II'a, IIIb and III'b, or derivatives thereof:



[in which] wherein

Ar is an aryl radical, R<sub>2</sub> is an aryl radical, R'<sub>2</sub> is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical, R''<sub>2</sub> is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical, and GP is a protective group [are defined in one of claims 1 to 3 and 5], and

R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical.

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FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
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13. (Once Amended) [Compounds] A compound according to one of claims [claim] 12 or 14, [characterized in that] wherein R is [one of the enantiomers of the] a menthyl radical enantiomer, [in particular] optionally (+)-menthyl.

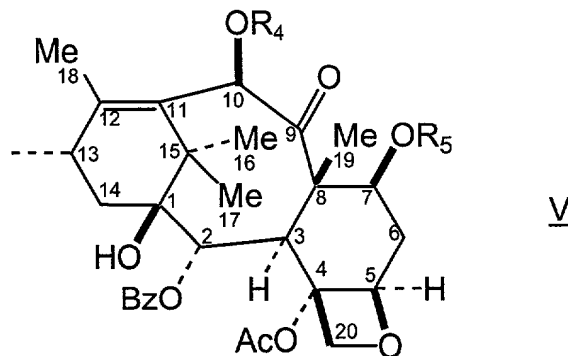
14. (Once Amended) [Compounds] A compound according to [either of claims] claim 12 [and 13], [characterized in that] wherein the cis- $\beta$ -phenylglycidate derivative of general formula I is of (2R,3R) configuration, and the derivatives of general formulae IIa, [IIb,] IIIb and III'b are of (2R, 3S) configuration.

17. [Process for the preparation of taxanes] A process for preparing a taxane of general formula IV,

C-B IV

[in which] wherein

B represents a radical of general formula V



[in which] wherein

Ac [represents the] is an acetyl radical,

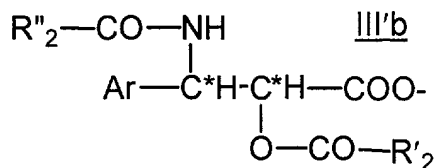
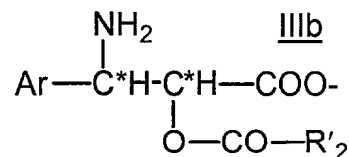
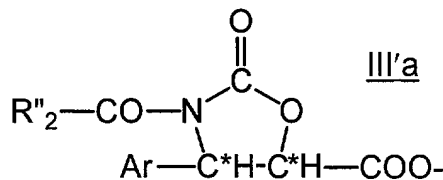
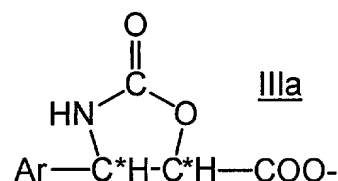
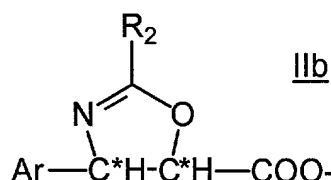
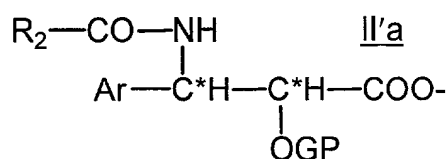
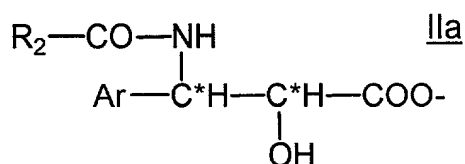
Bz [represents the] is a benzyl radical,

Me [represents the] is a methyl radical,

R<sub>4</sub> [represents] is an acetyl radical, or a protective group for the hydroxyl functional group, represented by GP1, [and]

R<sub>5</sub>[, represents] is a protective group for the hydroxyl functional group represented by GP2, wherein GP1 and GP2 are chosen independently of one another from conventional protective groups employed in a hemisynthesis of taxanes, and

C [represents] is a side chain chosen from [the radicals of following] formulae IIa, II'a, IIb, IIIa, III'a, IIIb, and III'b:

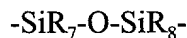


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& DUNNER, L.L.P.  
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[in which] wherein Ar is an aryl radical, R<sub>2</sub> is an aryl radical, R'<sub>2</sub> is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical, R''<sub>2</sub> is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical, and GP is a protective group, [are defined above, by esterification of] comprising esterifying an appropriate baccatin III derivative of general formula V, carrying a C-13 hydroxyl functional group, with [one of the derivatives] a derivative of formulae IIa, II'a, IIb, IIIa, III'a, IIIb [and] , or III'b, [for which] wherein R represents a hydrogen atom, [obtained by the process according to claim 11] and is obtained by controlled saponification.

18. (Once Amended) [Process] A process according to claim 17, [characterized in that] wherein the GP1 and GP2 protective groups are[, independently of one another, conventional groups employed in the hemisynthesis of taxanes, such as] independently chosen from trialkylsilyls, [or] TROC, [or] linear or branched bulky haloalkoxycarbonyl radicals comprising at least one halogen atom, acyl radicals in which the carbon [a] α to the carbonyl functional group carries at least one oxygen atom, or a trialkylgermanyl radical, or GP1 and GP2 together form a divalent radical of formula



[in which] wherein

R<sub>7</sub> and R<sub>8</sub>, independently of one another, each represent a sterically hindered alkyl radical.

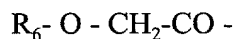
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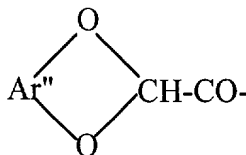
19. [Process] A process according to either one of claims 17 [and] or 18, [characterized in that] wherein the acyl radicals in which the carbon [a] α to the carbonyl functional group carries at least one oxygen atom are chosen from

- alkoxy- or aryloxyacetyl radicals of formula



wherein [in which]  $R_6$  [represents] is a sterically hindered alkyl radical, a cycloalkyl radical, or an aryl radical,

- or arylidenedioxyacetyl radicals of formula



wherein [in which]  $Ar''$  represents an arylidene radical.

20. (Once Amended) [Process] A process according to claim 19, [characterized in that] wherein:

the sterically hindered alkyl radical is a linear or branched  $C_1-C_6$  alkyl radical, substituted by at least one [or more] bulky [substituents] substituent chosen from halogens, [or] linear or branched  $C_1-C_6$  alkyl, linear or branched  $C_1-C_6$  alkoxy, [or]  $C_3-C_6$  cycloalkyl, and [or] aryl radicals,

the cycloalkyl radical is a  $C_3-C_6$  cycloalkyl radical, optionally substituted by at least one [or more] bulky [substituents] substituent independently chosen from halogens, [or] linear or

branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy, [or] and aryl radicals[, preferably a cyclohexyl radical substituted by one or more linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl radicals, for example menthyl, its racemate or its enantiomers and their mixtures in all proportions],

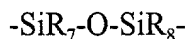
the aryl radical is a phenyl, naphthyl, anthryl or [phenantryl] phenanthryl radical, optionally substituted by at least one [or more] bulky [substituents] substituent chosen from halogens, [or] linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy, or aryl radicals, [in particular the phenyl radical, preferably a phenyl radical optionally substituted by one or two above bulky substituents ortho- and ortho'- to the ether bond,] and

the arylidene radical is a phenylene, naphthylene, anthrylene or phenanthrylene radical, optionally substituted by at least one [or more] bulky [substituents] substituent chosen from halogens, [or] linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy, and [or] aryl radicals[, in particular the phenyl radical].

21. (Once Amended) [Process] A process according to either one of claims 17 [and] or 18, [characterized in that] wherein R<sub>4</sub> represents an acetyl radical, and GP2 [represents] is chosen from a trialkylsilyl, 2,2,2- trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2,2,2,1-tetrachloroethoxycarbonyl, 2,2,2-trichloro-*t*-butoxycarbonyl, trichloromethoxycarbonyl, phenoxyacetyl, and [or] trialkylgermanyl [radical] radicals.

22. (Once Amended) [Process] A process according to either one of claims 17 [and] or 18, [characterized in that] wherein R<sub>4</sub> represents a GP1 group, and GP1 and GP2 [represent]

are independently chosen from a 2,2,2-trichloroethoxy-carbonyl [or] and a phenoxyacetyl radical, or together form a divalent radical of formula



in which R<sub>7</sub> and R<sub>8</sub> each represent an isopropyl radical.

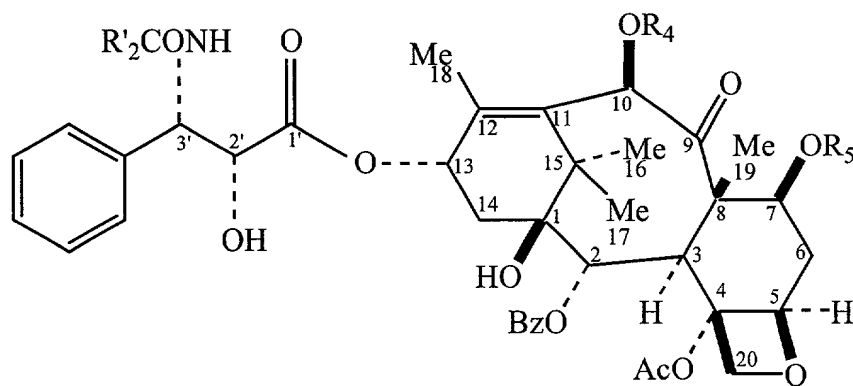
23. (Once Amended) [Process] A process according to [one of claims] claim 17 or 18 [to 21], [characterized in that] wherein

C [represents] is a radical of formula IIa with Ar<sub>3</sub> [and]

R<sub>2</sub> [representing] is a phenyl radical; and

R<sub>4</sub> [represents] is an acetyl radical.

24. (Once Amended) [Process] A process according to [one of claims] claim 17 or 18 [to 23], [characterized in that, subsequently,] further comprising deprotecting the hydroxyls of the derivatives of general formula IV [are deprotected] and[, if appropriate,] optionally, simultaneously or separately, opening the oxazoline ring of the radicals of formula IIb or IIIa [is opened, in order to produce] wherein a taxane derivative of general formula VI is produced



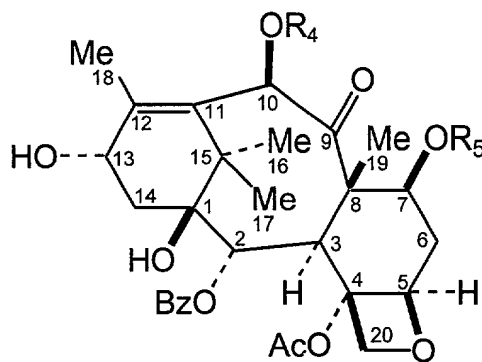
[in which] wherein

Ac is an acetyl radical, Bz is a benzyl radical, Me is a methyl radical, and R'<sub>2</sub> is an aryl radical, a lower alkyl radical, or a lower perhaloalkyl radical, [are defined in one of the preceding claims,]

R<sub>4</sub> represents a hydrogen atom or an acetyl radical, and

R<sub>5</sub> represents a hydrogen atom.

26. (Once Amended) [Baccatin III derivatives] A baccatin III derivative which [are] is of use in the hemisynthesis of taxanes, [characterized in that they are] chosen from [the] derivatives of general formula V



[in which] wherein

Ac [represents the] is an acetyl radical,

Bz [represents the] is an benzyl radical,

Me [represents the] is a methyl radical,

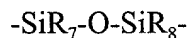
R<sub>4</sub> [represents] is an acetyl radical or a protective group for the hydroxyl functional group

represented by GP1,

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FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000

R<sub>5</sub> [represents] is a protective group for the hydroxyl functional group represented by GP2, [and] wherein GP1 and GP2 are[,] selected independently of one another[,] from bulky haloalkoxycarbonyl radicals, with the exception of [TrOC] TROC, acyl radicals in which [the] a carbon [a] α to the carbonyl functional group carries at least one oxygen atom, [or] and trialkylgermany radicals, or GP1 and GP2 together form a divalent radical of formula



[in which] wherein

R<sub>7</sub> and R<sub>8</sub> selected independently of one another, represent a sterically hindered alkyl radical.

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FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N. W.  
WASHINGTON, DC 20005  
202-408-4000